Prolonged complete remission of metastatic HER2-positive breast cancer after continuous trastuzumab treatment: a case report and review of the literature

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DAY-TO-DAY PRACTICE

Prolonged complete remission of metastatic HER2-positive breast cancer after continuous trastuzumab treatment: a case report and review of the literature

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Abstract Metastatic breast cancer is considered an incurable disease. Targeted treatments against the human epidermal growth factor receptor 2 (HER2), however, significantly improve survival in patients with metastatic HER2-positive breast cancer. Some patients may respond with prolonged complete remission. Evidence on safety of long-term trastuzumab and risk of relapse after trastuzumab cessation is limited. We present a case of an 81-year-old patient with HER2-amplified metastatic breast cancer (MBC) in the liver. Following taxane-based chemotherapy in combination with trastuzumab after local treatment resulted in a complete radiological remission after 21 months of trastuzumab maintenance therapy. The patient remains in complete remission 6 years later and continues to receive trastuzumab as maintenance therapy. Prolonged remission in cases with complete response under trastuzumab-based regimens for metastatic HER2-positive breast cancer can be observed in some patients. Reviewing the few available cases published in the literature, these patients share some common characteristics: hormone receptor negative disease and metastases to the liver. There is no evidence that trastuzumab maintenance treatment can be safely interrupted after a certain time period.

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Abbreviations

OS	Overall survival
HER2	Human epidermal growth factor receptor 2
EGFR	Epidermal growth factor receptor
MBC	Metastatic breast cancer
BC	Breast cancer
TTP	Time to progression
CHT	Chemotherapy
HR	Hormone receptor

Introduction

Trastuzumab added to standard chemotherapy has improved disease-free and overall survival (OS) among patients with human epidermal growth factor receptor 2 (HER2)-amplified metastatic breast cancer (MBC) [1]. However, HER2-amplified MBC is an aggressive breast cancer subtype, and despite the development of anti-HER2 targeted treatments, the majority of patients progress within 12–18 months [2, 3]. Before the use of trastuzumab, the natural course of this subtype had a poor prognosis. Due to the use of trastuzumab, the prognosis of hormone-receptor (HR)-negative/HER2-positive disease has significantly improved and OS even largely exceeds the one of HR-negative/HER2-negative disease [4]. In HR-positive disease, the results are controversial; whereas Dawood et al. show a similar OS between HER2-positive and HER2-negative subtypes, some say the OS of HER2-positive subtypes exceeds the OS of HER2-negative subtypes [5]. Generally, the OS of estrogen-receptor (ER)-positive/HER2-positive breast cancer

has the best prognosis [5]. Only very few patients with a HER2-amplified MBC experience a prolonged remission. This case report describes a patient with a primary metastatic HR-negative/HER2-positive breast cancer. Six years after locoregional and systemic treatment with paclitaxel and trastuzumab, she remains in complete remission under trastuzumab maintenance therapy.

Case presentation

We present the case of an 81-year-old woman with primary metastatic HER2-positive breast cancer. Two liver metastases in segment IVa and VII measuring 3.3 cm each (Fig. 1) were detected in radiological staging after segmentectomy and axillary lymph node resection for her pT2 (32 mm) pN2a (5/15) G3 ER/PR-negative HER2-positive breast cancer. Postoperative chemotherapy with 4 cycles of paclitaxel (80 mg/m^2 day 1, 8, and 15) and trastuzumab weekly (4 mg/kg loading dose followed by 2 mg/kg maintenance dose weekly) was administered. Complete radiological response and a non-pathological CA15-3 value were obtained after 21 months of trastuzumab maintenance treatment. The patient remains in complete remission 6 years after primary treatment of metastatic disease and continues to receive trastuzumab as maintenance therapy. Despite cardiovascular comorbidities such as arterial hypertension, hyperlipidemia, and activated protein C resistance with recurrent deep vein thrombosis and a family history of myocardial infarct, there were no morphological or functional cardiac changes during the trastuzumab therapy.

Discussion

HER2-targeted therapies have significantly improved disease-free interval and overall survival in HER2-amplified BC,

Fig. 1 Abdomen ultrasound with liver metastases

Table 1 Overview of published cases with prolonged complete remission

Case report	Patient's age	HR status	Metastases	CHT with trastuzumab	TTP with trastuzumab maintenance	Trastuzumab maintenance	Follow-up
Present case	81	ER-/PR-	Hepatic	Paclitaxel and trastuzumab	Up to today: 6 years	Maintenance	In CR
[23]	34	ER-/PR-	Hepatic	Vinorelbine, gemcitabine, and trastuzumab	Up to today: 7 years	Maintenance	In CR
[21]	36	ER-/PR-	Hepatic	Paclitaxel and trastuzumab	3 years	Stopped at progression	Brain metastases
[22]	46	ER-/PR-	Hepatic and bone	Trastuzumab monotherapy	Up to today: 8.5 years	Maintenance	In CR
[25]	53	ER+/PR-	Hepatic	1st line: paclitaxel and trastuzumab, 2nd line: capecitabine and lapatinib	17 months 4 years with lapatinib maintenance	Stopped at 2nd progression	In CR with lapatinib alone
[24]	54	ER-/PR-	Hepatic	Docetaxel, pertuzumab, and trastuzumab	Up to today: 6 months	Trastuzumab and pertuzumab maintenance	In CR
[20]	49	ER+/PR+	Bone marrow	Paclitaxel, cisplatin, and trastuzumab	Up to today: 5 years	Trastuzumab and letrozole maintenance	In CR

CR complete remission, *TTP* time to progression, *CHT* chemotherapy, *HR* hormone receptor

which was associated with an aggressive biological behavior and a shorter disease-free interval and OS [6, 7]. Trastuzumab, however, has improved the clinical outcome of patients with HER2-amplified BC beyond that of certain HER2-negative subtypes [8, 4, 9].

First-line treatment for HER2-amplified MBC commonly contains a taxane-based monochemotherapy regimen in combination with single or dual HER2 blockage [1, 6, 10]. Currently approved anti-HER2-directed drugs for the treatment of HER2-positive MBC in the USA are anti-HER2 monoclonal antibodies, such as trastuzumab, pertuzumab and ado-trastuzumab emtansine, and lapatinib, an inhibitor of HER2 and EGFR. Recently, dual blockage of HER2 has been widely accepted, after a phase III trial of trastuzumab/docetaxel ± pertuzumab showed the combination to be superior to the monotherapy [1].

Following response to first-line chemotherapy in combination with anti-HER2 treatment, maintenance treatment with an anti-HER2 drug until progression of disease remains currently the standard of care. The optimal duration of trastuzumab administration after achieving complete remission of metastatic breast cancer remains, however, unknown. Studies analyzing clinical benefits with trastuzumab in disease beyond progression underline the significant improvements of OS by maintaining the trastuzumab treatment, indicating that progression of disease is not necessarily due to a resistance to trastuzumab [11, 12]. In the Royal Marsden experience [13], Waddell et al. provide evidence that trastuzumab continuation beyond progression is of clinical benefit: 59 % of the patients with clinical or radiological response achieved a stable disease or better with a median TTP of 24 weeks and a median OS of 19 months. This experience confirms other analysis with patients who received second-line trastuzumab-based chemotherapy for metastatic disease. They achieved a median OS significantly better than those discontinuing trastuzumab at disease progression [13, 14–17].

The long-term use of trastuzumab raises concerns about cardiotoxicity. An early pivotal trial showed a high incidence of cardiac events under the treatment of trastuzumab, especially when associated with anthracyclines [8]. These adverse effects were mainly reversible. In studies of trastuzumab treatment beyond progression, cardiac events are uncommon and mostly asymptomatic [11, 18, 19].

After reviewing the published case reports (Table 1) on prolonged complete response following metastatic HER2-amplified disease, it is important to note that in all cases anti-HER2 maintenance treatment has been continued, either with trastuzumab alone [20–23] in combination with pertuzumab [24] or with lapatinib alone [25]. In this last case, trastuzumab was stopped at a 2nd progression of disease to achieve a complete remission with lapatinib maintenance therapy [25]. The longest reported relapse free time with trastuzumab maintenance treatment is 8.5 years [22]. So far, no case has been published with prolonged complete remission after cessation of anti-HER2 maintenance therapy. All but one case of complete remission describe metastases in the liver. One case describes bone marrow metastases with complete response and long-term remission under trastuzumab maintenance treatment [20]. Gene expression studies on response to trastuzumab or lapatinib have shown that HER2-enriched intrinsic profile (ER/PR negative) have higher response rates, as in our case, than HER2 amplified tumors classifying to the luminal intrinsic subtype [26]. Accordingly, in the neoadjuvant setting of HER-2 amplified BC, ER/PR negativity is an independent predictive marker for response to trastuzumab-based chemotherapy in terms of complete pathological response [27].

Conclusion

Prolonged remission in cases with complete response under trastuzumab-based treatment for metastatic HER2-amplified breast cancer is predominantly seen within patients with hormone receptor negative disease and liver metastases, as in the present case. There is no evidence of prolonged complete remission after trastuzumab cessation. Cardiotoxicity has not been reported to be of concern in the presented cases receiving trastuzumab maintenance treatment for more than 5 years.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the editor of this journal.

Conflict of interest The authors declare that they have no conflict of interest.

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